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14. ABSTRACT

Surgery for breast cancer includes removal of the breast tumor along with axillarylymph nodes. Unfortunately, a relatively common side effect following axillary lymph node dissection (ALND) is upper-extremity lymphedema. The purpose of this study is to identify risk factors for lymphedema among women with breast cancer surgery. Specific aims include identifying risk factors for lymphedema and comparing quality of life (QOL) for women who have and do not have lymphedema. A case-control study will be conducted with 200 participants. Cases will be identified in the physical therapy or cancer centers. Controls will be identified using the oncology registry and include patients with breast cancer surgery who have not developed lymphedema. Risk factors and severity of lymphedema will be assessed with the Measure of Arm Symptom Survey (MASS), a patient-competed survey. QOL will be collected with the SF-36. Treatment risk factors will be obtained from the oncology registry. This study will determine which factors are important in lymphedema development.

15. SUBJECT TERMS
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I. Introduction

Lymphedema is a common problem for patients diagnosed with breast cancer, with an estimated 6 – 35% developing it sometime after breast cancer treatment.[1-15] In 2006, it is estimated that 214,640 women will be diagnosed with breast cancer, and 88% of these women will survive at least 5 years.[16] The reported incidence of lymphedema varies with the length of follow-up, the measurement techniques, and other patient and treatment-related factors.[5] It can range from mild to severe, and can be a chronic condition that affects patients' quality of life for years after cancer surgery. Patients are interested in learning how to prevent lymphedema because it is one of the more feared side effects following completion of treatment.

A less invasive procedure, sentinel lymph node dissection (SLND), has shown a reduction in reported lymphedema and other arm symptoms.[9, 22 - 25] In a study conducted at Park Nicollet Institute, 4.7% of SLND patients reported arm swelling at six months after surgery versus 19.5% of ALND patients ($p < .001$).[22] However, patients are not eligible for SLND if they have clinically positive nodes, a pathologically positive sentinel node, or if the surgeon is unable to locate the sentinel lymph node.

Several treatment-related factors have been associated with lymphedema including the extent of axillary dissection, axillary radiation therapy after surgery, type of surgery, and the presence of infection in the ipsilateral arm.[2-6,12,26-31] Several patient-related factors have also been evaluated for their association with lymphedema in breast cancer patients including body mass index, weight training exercise, airline travel, hypertension, diabetes, smoking and age at breast cancer diagnosis, and findings have been inconsistent for these factors.[1,3-5,12,14,15,29,32-35]

Previous studies have several limitations. Most of the studies have a small sample size without a comparison group, making it difficult to determine which factors are significantly associated with lymphedema. The surgery and treatments for breast cancer have changed in recent years, with a higher proportion of patients now having lumpectomy, sentinel lymph node dissection, and adjuvant treatment. Women are advised to avoid lifting weights, constrictive pressure, and activities that could lead to arm injury or infection, but most of this advice is based on very limited data. Therefore, there is a need for additional studies to identify factors that contribute to the development of lymphedema in breast cancer patients.

II. Body

Specific aims. The primary specific aim of this study is to identify risk factors for lymphedema among women who have had axillary surgery for breast cancer. Secondary aims are: 1) to evaluate which factors predict moderate/severe lymphedema in patients who have lymphedema, 2) to describe patients' rating of the interference with daily life caused by lymphedema, 3) to compare the reported quality of life using the SF-36 (Short Form-36) for patients with and without lymphedema, 4) to compare arm circumference measurements to patient-reported lymphedema, and 5) to identify the cause(s) to which patients attribute their lymphedema.

Study design. This study uses a matched case-control design, which permits identification of risk factors that are present more often in lymphedema cases than in controls who have had breast cancer surgery but have not developed lymphedema. Lymphedema cases will be identified at the time they present to the physical therapy department or cancer center at five participating institutions – Park Nicollet Health Services (Methodist Hospital), Fairview-University Medical Center, Fairview Southdale Medical Center, the Humphrey Cancer Institute, and HealthEast Care System. The protocol and consent forms for the study were reviewed and approved by the participating institutional review boards and the Department of Defense HSRRB.

Research subjects. Eligibility criteria for cases include: a clinical diagnosis of lymphedema, unilateral axillary surgery for invasive breast cancer, no known metastatic disease present, and ability and willingness to give consent. Control participants will be identified using the oncology registry. Eligibility criteria for controls include: no upper extremity lymphedema, unilateral axillary surgery for invasive breast cancer, no known metastatic disease, and ability and willingness to give consent. Controls will be matched to cases on date of axillary surgery (within 3 months) and type of axillary dissection (sentinel versus axillary lymph node dissection). Controls will not be matched on age or other factors because matching on a variable precludes the possibility of assessing its role as a potential risk factor. Using previous literature to estimate effect size, sample size for this study is set at 100 cases and 100 controls.

Questionnaires. The Measure of Arm Symptom Survey (MASS-Version 3) will be administered to cases and controls as a subjective measure of lymphedema. Breast cancer patients with lymphedema (i.e., cases) are asked to complete a revised questionnaire (MASS – Version 3 lymphedema) with questions referencing the date of the onset of arm swelling. Potential lymphedema risk factors are assessed in the MASS including diabetes, hypertension, smoking, past shoulder injury, flexibility exercises, strength training exercises, medical procedures, arm/hand injury, airline travel, body mass index (BMI) and occupation. The questionnaires address the severity of symptoms by having patients rate them on a 5-point Likert-type scale from no swelling to very severe swelling. The degree of interference with life activities will be assessed using a similar 5-point scale of "not at all" to "very much". The MOS 36-Item Short-Form Health Survey (SF-36) will be administered to cases and controls to assess general health-related quality of life. This questionnaire uses two summary component scales (physical and mental), and higher scores reflect greater quality of life. To assess test-retest reliability, a second MASS questionnaire was mailed to the first 24 cases in the study within two weeks after the initial questionnaires were completed. After reliability information was collected on the first 24 cases, the questionnaires have been administered on a one-time basis.

Setting. Patients are being recruited from five clinics in Minneapolis, Minnesota. Park Nicollet Health Services (PNHS) is a large multi-specialty clinic with approximately 370 breast cancer cases diagnosed annually. Fairview-University Medical Center (F-UMC) is a National Cancer Institute-designated Comprehensive Cancer Center with approximately 150 breast cancer cases diagnosed annually. Fairview Southdale Medical Center (FSMC) is affiliated with a regional hospital with approximately 300 breast cancer cases

diagnosed annually. The Humphrey Cancer Institute (HCI) is affiliated with North Memorial Medical Center, a regional hospital with approximately 320 breast cancer cases diagnosed annually. HealthEast Care System includes St. John's Hospital and St. Joseph's Hospital in St. Paul, Minnesota. It was added as a recruitment site at the end of 2005 to increase enrollment. Adequate numbers of control patients are available because of the large number of breast cancer patients diagnosed annually.

Data analysis. Univariate analysis will be conducted to describe the characteristics of cases and controls. Chi-square tests will be used to compare cases and controls on potential risk factors for lymphedema. Conditional logistic regression analysis will be used to model the association of potential risk factors with the presence of lymphedema.

III. Key Research Accomplishments

- Preparations to begin the study
    - Determined staff and roles on the study
    - Reviewed and revised MASS instrument with input from the lymphedema education group
    - Presented study and consent forms to 3 local IRBs (Fairview IRB is used for both Fairview University and Fairview Southdale sites; Park Nicollet Institute IRB for the Community Oncology Programs is used for Park Nicollet Health Services and HealthEast Care Systems) and obtained approval to begin enrollment
    - Received approval from the USAMRMC HSRRB to enroll research subjects
    - Developed database and data dictionary for the study

- Accrual and data collection
    - Between 12/03 and 9/06 a total of 72 participants have been enrolled (55 participants from Methodist Hospital, 5 participants from the Humphrey Cancer Institute, 8 participants from Fairview, and 4 participants from HealthEast Care System).
    - Matched controls have been identified for the 72 cases and surveys have been sent to controls.
    - Arm measurement have been taken by the physical therapists and recorded on all cases.
    - Reliability MASS questionnaires were mailed to enrolled cases within two weeks of enrollment.
    - Treatment data have been collected from the physical therapy or medical records on all participants.
    - IRB annual approval was granted from the local IRBs and the USAMRMC HSRRB to continue enrollment of research subjects at the five institutions.
    - Entered demographic and treatment data for the cases and controls currently accrued and summarized data (see Table 1).

Table 1. Demographic and treatment data for cases and controls enrolled to date

Factors	Cases (n = 72)	Controls (n = 52)
Mean age	58.2	60.0
Mean # of nodes removed	14.4	14.4
Mean # of nodes positive	4.3	1.6
% receiving mastectomy	77.5%	48.0%
% receiving reconstructive surgery	26.1%	22.4%
% receiving radiation therapy	69.0%	73.5%
% receiving chemotherapy	85.5%	61.2%
% receiving hormone therapy	68.1%	80.0%

- Amendments have been reviewed and approved by the three IRBs and the HSRRB at the DoD for the study:
    - Amendment #1 (4/24/03) made administrative changes in the study which clarified eligibility criteria, changed study design to a matched case control design with conditional logistic regression, modified the MASS to version 3.
    - Amendment #2 (10/14/03) revised the subject letter, and made administrative changes in the protocol.
    - Amendment #3 (2/17/04) changed the eligibility criteria from 10% to 5% difference between arms in patient's total arm girth.
    - Amendment #4 (7/9/04) changed the eligibility criteria from 5% to "a clinical diagnosis of lymphedema" and changed the enrollment procedures for controls to absence of a clinical diagnosis of lymphedema.
    - Amendment # 5 (5/6/05) changed recruitment goal to 100 cases and 100 controls, includes cases identified in the cancer centers as well as the lymphedema centers, and includes both incident and prevalent lymphedema cases.
    - Amendment # 6 (9/29/05) added HealthEast Care System to the list of recruitment sites.

IV. Reportable Outcomes

- Research training of the candidate
    - Karen Swenson, RN, PhD, AOCN completed her coursework requirements and her dissertation and final defense for her nursing

doctoral program at the University of Minnesota (41 credit hours). The completion date was 4/18/06.

- Enrollment of research participants
  - Enrollment of 72 lymphedema cases and 52 controls
  - Completion of SF-36 and MASS questionnaires on all cases and controls enrolled to date
  - MASS reliability questionnaires were completed by 24 case participants
- Meetings and training with participating sites
  - Regular meetings have been conducted at the participating sites to discuss training, enrollment issues, and possible changes to improve site enrollment.
  - Several changes have been made in the protocol (Amendments 1 – 6) to improve the enrollment process at the sites, including making changes in the eligibility criteria, revising and further defining the enrollment process, and ongoing training at all of the sites.
- Data entry is ongoing and is current for the cases and controls currently enrolled.
- A poster presentation P20-15 entitled "Predictors of lymphedema following breast cancer surgery" was presented at the Era of Hope Department of Defense Breast Cancer Research Program Meeting, June 8 – 11, 2005.

V. Conclusions

This research project has provided the candidate with a valuable learning experience in designing and conducting a case-control study. The candidate has successful completed her nursing doctoral program at the University of Minnesota. This grant has provided the candidate with experience in conducting a multi-center breast cancer study, managing the regulatory process, revising and validating the MASS questionnaire, recruiting and enrolling research participants, and collecting questionnaire data from participants.

Enrollment has been slower than projected in the Statement of Work. With the advent of sentinel lymph node dissection in 1999, the lymphedema incidence after breast cancer surgery has decreased considerably.[22,36] To increase enrollment, both incident and prevalent cases are now eligible. This has improved the enrollment rate - a total of 48 cases have been enrolled during the past year (4 participants/month). Another modification includes decreasing the study sample size from 200 to 100 matched pairs. The power and minimal effect size with 100 matched pairs have been recalculated and are listed below in Table 2. The revision in sample size decreases the power to detect the estimated effect size of some of the variables, but remains at an acceptable level for most of the variables. A request has been submitted for a 12-month no cost extension so that an adequate sample size can be achieved.

The overall goal of this study is to identify modifiable risk factors for lymphedema in patients who have had breast cancer surgery. This is an important area of study because currently there is little research guiding lymphedema prevention recommendations. If modifiable risk factors are identified in this study, they will lead to further research by the

investigators on the effectiveness of education and other strategies to prevent lymphedema after breast cancer treatment.

Table 2. Sample size calculations are based on 100 matched pairs (200 participants). Calculations were made to determine the power to detect the estimated effect size, and the minimal effect size (OR) that the study could detect. Six variables are added, and the minimal effect size is calculated for each variable.

Variable	Estimated Odds Ratio	Power (1-β)	Minimal Detectable Effect (OR)
RT (yes/no)[29]	2.85	.91	2.23
Axillary RT (yes/no)[29]	6.31	.99	2.30
Infection (yes/no)[29]	16.78	.99	2.96
Tumor size (T2,T3,T4 versus T1)[37]	1.78	<.5	2.23
Nodal status (N1,N2,N3 versus N0)[37]	1.82	.55	2.23
Dissection (ALN vs. SLN)[23]	6.74	.99	2.30
Weight (BMI>27.2 vs. ≤27.2)[29]	1.49	<.5	2.23
Tumor location (UO vs. other)[23]	2.19	.76	2.23
Age (>55 vs. ≤55)[6]	1.89	.60	2.23
Smoking			2.30
Hypertension			2.30
Diabetes			2.96
Arm/shoulder injury			2.96
Stretching			2.30
Strength training			2.96

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